Treatment of Hypertension

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Cardiopulmonary module

INTENDED LEARNING OBJECTIVES (ILO)

Lecture 3:

1. Explain the role of adrenergic blockers and inhibitors in the treatment of hypertension
2. Identify the role of arteriodilators in the treatment of hypertension
3. List the uses and adverse effects of arterio-dilators

7- Sympathetic Depressants

Sympathetic depressants are used in treatment of hypertension & discussed before in the autonomic nervous system. They include:

- Centrally Acting Sympathetic Depressants: α-2 Agonists (Methyldopa) & imidazoline I-1 receptor agonists (Clonidine).
- Adrenergic Neuron Blockers: Reserpine & Guanethidine.
- Adrenergic Receptor Blockers: Prazosin (α1-blocker) & beta-blocker.

a. α-ADRENOCEPTOR–BLOCKING AGENTS

- ***Prazosin, doxazosin, and terazosin*** **produce a competitive block of α_1 adrenoceptors.**

Mechanism of action: **They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.**

Uses:

- **α_1-Blockers may be used to treat mild to moderate hypertension.**
- **They are more effective when used in combination with other agents, such as a β blocker and a diuretic, than when used alone.**
- **They are used primarily in men with concurrent hypertension and benign prostatic hyperplasia**

Adverse effects

1. **First-dose syncope**: the first dose should be small and should be administered at bedtime.
2. **Reflex tachycardia**: less with the selective alpha 1 blockers than it is with non-selective alpha 1 and alpha 2 blockers

Concomitant use of a β-blocker may be necessary to blunt the short-term effect of reflex tachycardia.

Cardiopulmonary Module

b- Centrally Acting Adrenergi Drugs

(Alpha 2 agonists)

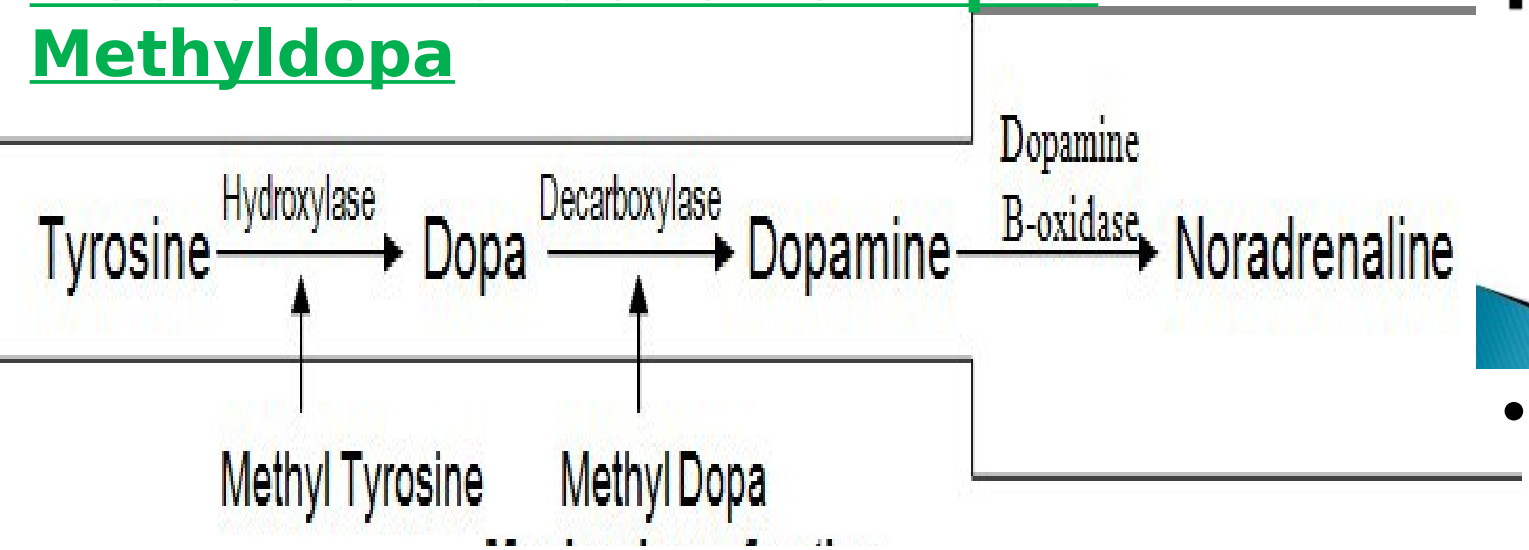
Methyldopa – Clonidine - Guanfacine - Guanabenz

Alpha methyl dopa

Pharmacokinetics

- Absorbed orally, Can pass B.B.B.
- Transformed to alpha methyl noradrenaline

Mechanism of action of Alpha Methyldopa



3. Drugs which interfere with the synthesis of NA (Methyldopa)

- **Methyldopa is a dopa decarboxylase competitive inhibitor → prevention of the conversion of dopa to dopamine → *inhibition of the biosynthesis of NA***
- **Methyldopa is metabolized to α-methyl NA which is stored in the sympathetic nerve endings → *displacement of NA and acts as a false transmitter***
- **also inhibit biosynthesis of *serotonin (5-HT) by inhibition* of decarboxylation of 5-**

Mechanism of action of Alpha Methyldopa

1-Methyl dopa inhibit dopa decarboxylase enzyme competes with dopa leading to decrease synthesis of nor adrenaline.

2- formation of methyl noradrenaline, acting as a 'False transmitter'.

Methyl NA , stimulates (α2) receptors:

- **Stimulate *α* 2 receptors in brain stem ⇨ decrease sympathetic flow from CNS.**
- **Stimulate *α* 2 receptors in the kidney ⇨ Decrease Release of renin.**
- **Stimulate *α* 2 receptors at the adrenergic ner**
  ⇨ ⇩ NA release.

3- Central sedative effect.

Uses of Alpha Methyldopa

- Hypertension with pregnancy.
- Mild and moderate hypertension especially in hypertension with renal insufficiency as it may improve renal blood flow.

Adverse Effects of Alpha Methyldopa

C.N.S.:

- Sedation.
- Night mares.
- Depression (impaired neuron function)
- Parkinsonism

Parasympathetic predominance:

-Bradycardia. -Nasal stuffiness. -Diarrhea.

-Postural hypotension (with large doses),

Other side effects of Alpha Methyldopa

- Liver toxicity.
- Positive Coomb's test

-Contraindication of Alpha Methyldopa

1- Depression. 2- Liver diseases.

Clonidine

Action of clonidine

Hypotension by **central** and **peripheral** action

a- Central action:

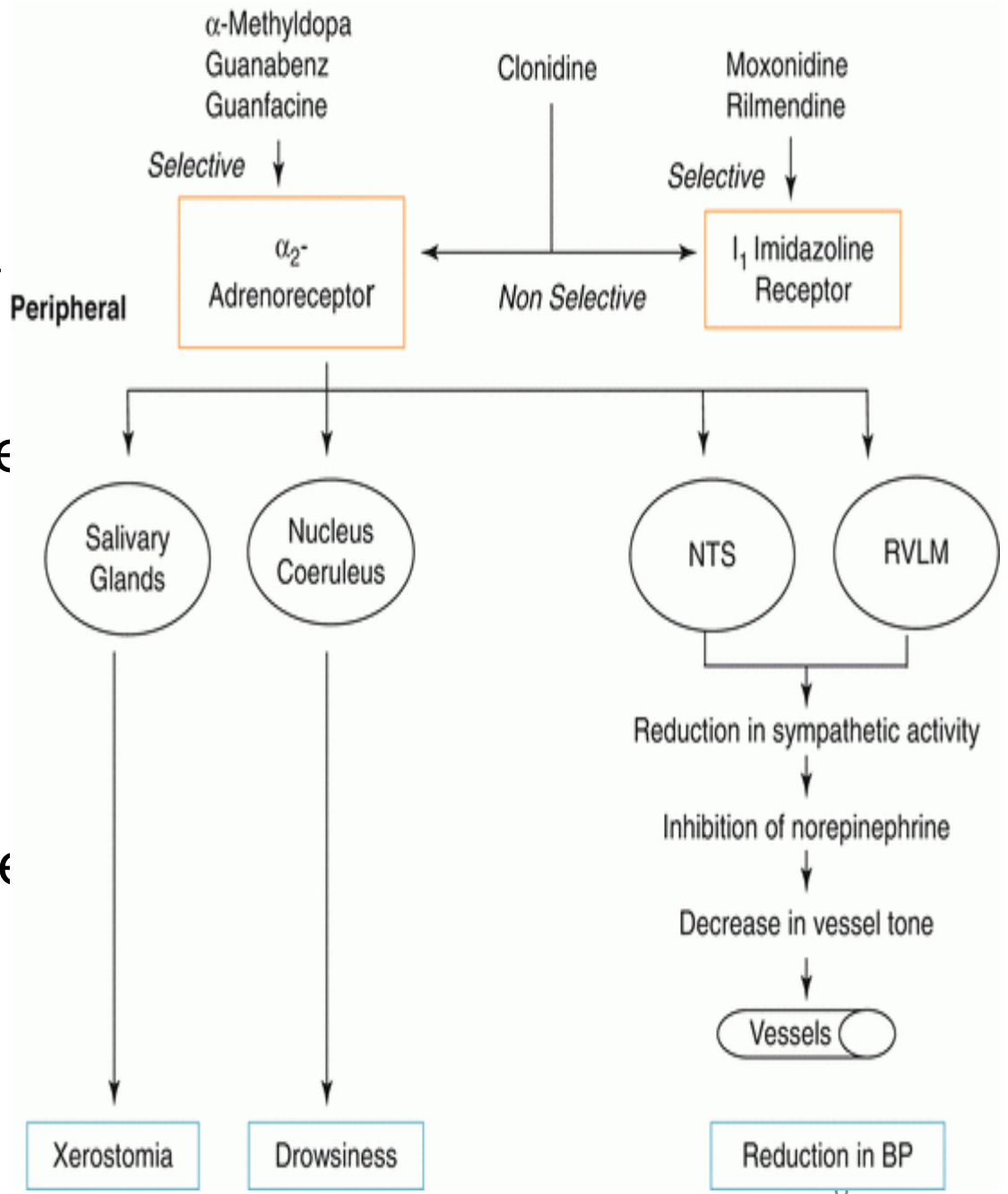
- Stimulate (α2) adrenergic and Imidazoline I-1 receptors in the brain stem→ inhibit V.M.C Decrease sympathetic outflow from C.N.S.→VD

b- Peripheral action:

- Stimulate pre-synaptic (α2) receptors lead to decrease releasing of Noradrenaline
- Anti-Renin

Effects:

- reduction of cardiac output due to decreased heart rate and relaxation of vessels,
- reduction in peripheral vascular resistance.
- decreased renal vascular resistance



Uses of clonidine

- Hypertension: mild and moderate (it increases renal blood flow)
- Prophylaxis: migraine headache.
- Used in morphine withdrawal

Combined with morphine in caudal anesthesia provides better anesthesia.

Adverse effects of clonidine

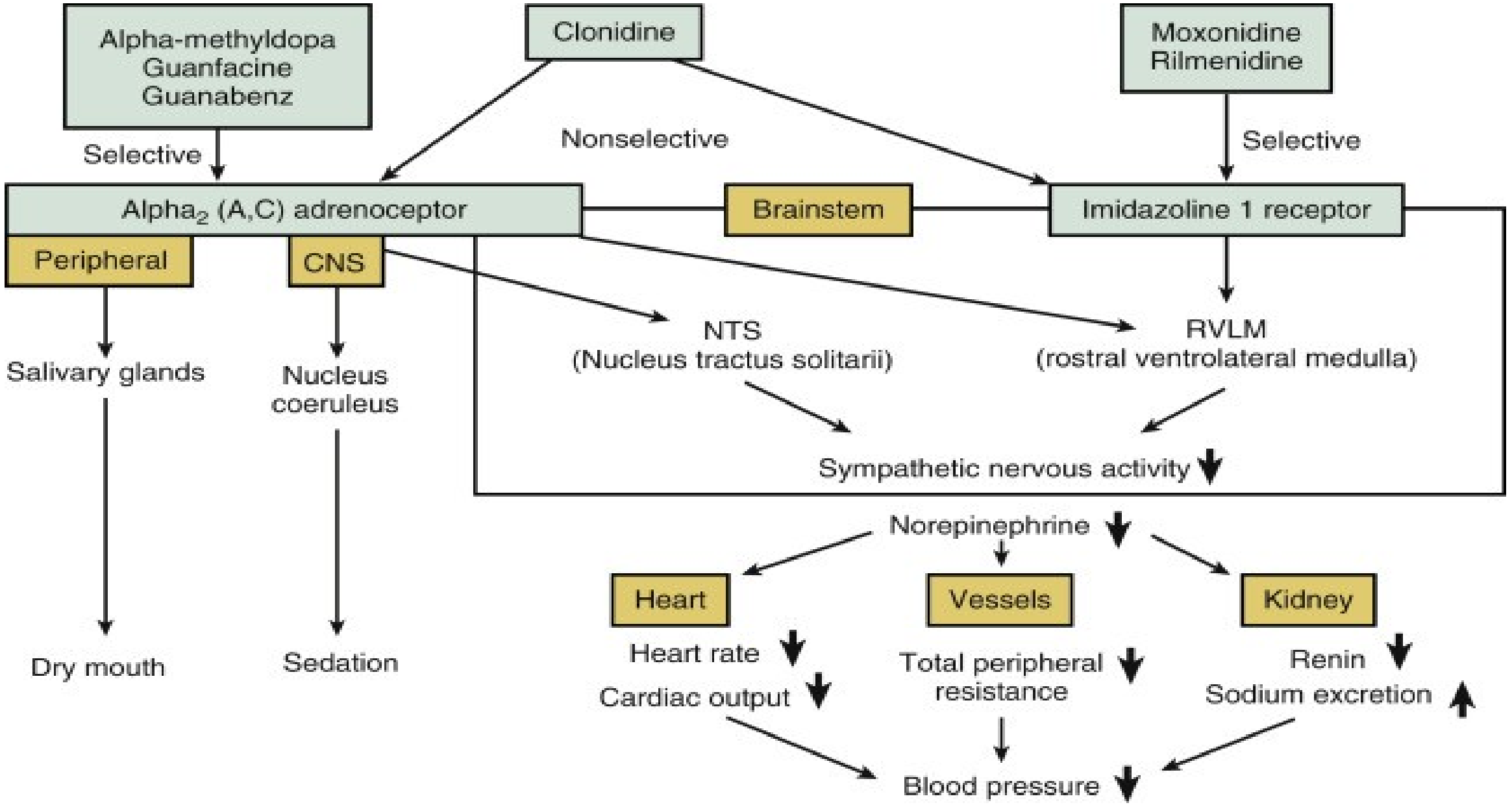
1- Dry mouth and Drowsiness (sedation) centrally mediated and dose-dependent and coincide temporally with the drug's antihypertensive effect.

2-Don't stop it suddenly → rebound hypertensive crisis. Treatment by Phentolamine

Guanfacine & Guanabenz

3- Bradycardia.

- More selective on α2 receptors with longer duration & less side effects: Less sedation, less dry mouth, less rebound hypertension.


Alpha-methyldopa
Guanfacine
Guanabenz
Clonidine
Moxonidine
Rilmenidine
Selective
Nonselective
Selective
Alpha2 (A,C) adrenoceptor
Brainstem
Imidazoline 1 receptor
Peripheral
CNS
Salivary glands
Nucleus coeruleus
NTS
(Nucleus tractus solitarii)
RVLM
(rostral ventrolateral medulla)
Sympathetic nervous activity
Norepinephrine
Heart
Vessels
Kidney
Heart rate
Cardiac output
Total peripheral resistance
Renin
Sodium excretion
Dry mouth
Sedation
Blood pressure

8. VASODILATORS

Classification

A) Direct Vasodilators:

1. Veno - Dilators: Nitrates. (See Angina).
2. Arterio - Dilators: Hydralazine-Minoxidil and Calcium channel blockers e.g. nifedipine
3. Mixed Dilators: Na^+ Nitroprusside

B) O t h e r s:

They modulate, stimulate or block endogenous mediators:

4. Renin-Angiotensin Aldosterone Antagonists e.g. Captopril.
5. Most of Autacoids: Histamine & Bradykinin
6. Sympathomimetics: Beta 2-Agonists e.g. Isoxsuprine and D1-Agonists e.g Fenoldopam.
7. Sympathetic Depressants e.g. Alpha1-blockers e.g. Prazosin.

- All the vasodilators that are useful in hypertension relax smooth muscle of arterioles, thereby decreasing systemic vascular resistance.
- Decreased arterial resistance and decreased mean arterial blood pressure compensatory responses, mediated by:
  - baroreceptors and the sympathetic nervous system
  - renin, angiotensin, and aldosterone
- Because sympathetic reflexes are intact, vasodilator therapy does not cause orthostatic

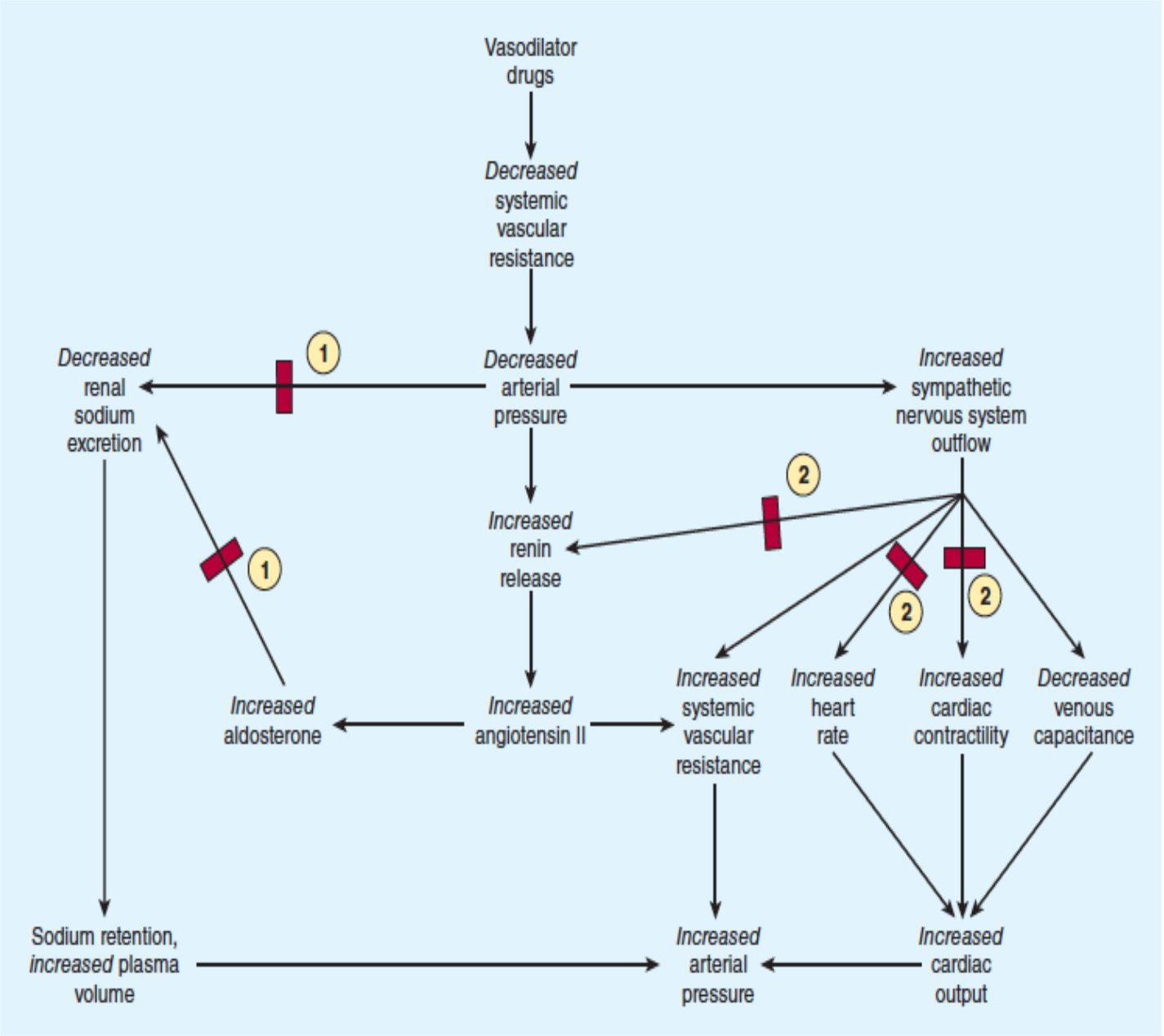


FIGURE 11–4 Compensatory responses to vasodilators; basis for combination therapy with β blockers and diuretics. ① Effect blocked by diuretics. ② Effect blocked by β blockers.

1-Hydralazine

Direct **Arteriolar** VD. May act through release of NO.
Decrease TPR, BP. (DBP > SBP) & After-load, Increase Stroke volume & COP in HF.
Undergoes acetylation in liver.
Idiosyncrasy slow acetylators are more prone to adverse effects.

Disadvantages Especially in Large dose & Slow Acetylators.

a- decrease BP. → reflex ↑ Sympathetic → ↑ Heart → Tachycardia & Angina

.

so contraindicated in:

-Angina (ADD beta-Blocker).

-Kidney → ↑Renin → Edema. (ADD Diuretic).

b- VD → Headache, Congestion & Flush.

c- Hypersensitivity (Allergic) Reactions: Reversible Rheumatoid arthritis & Lupus erythematosus-like syndrome. Skin rash & drug's fever.

d- Peripheral neuritis (in slow acetylators): Treat by Vit B6

Therapeutic Uses

1-Hypertension (ADD beta-blocker and/or Diuretic).

2- with nitrates in Heart Failure.

Congestive Heart Failure in Black patients

Hydralazine/isosorbide dinitrate fixed dose combination

- FDA approved to add to standard therapy for black Americans with congestive heart failure

(due to poor response to ACE inhibitors)

- should be considered for patients intolerant to ACE inhibitors & ARBs due to renal dysfunction

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Minoxidil

Minoxidil **(Prodrug)** → Minoxidil Sulfate (Active Metabolite):
Activate K+Channel : Hyperpolarization.
Potent, **O**ral, **L**ong acting, **D**irect **A**rterio-VD.

Disadvantages of Minoxidil

a- Decrease BP.
-Reflex stimulation of sympathetic flow: stimulate Heart: Tachycardia & Angina. **(C.I. in Anglia: ADD beta-blocker).**
-Kidney: increases Renin : Edema **(ADD Loop Diuretic).**
b- Hypertrichosis (++ hair growth).

Therapeutic Uses of Minoxidil

a- Severe Hypertension (ADD beta-blocker & Loop Diuretic).
b- Resistant Heart Failure.
c- Locally in Alopecia (Lotion & Cream)

Diazoxide

Direct Arteriolar VD. Activates K+-Channels.
Related to Thiazide Diuretics.

Disadvantages

a- Decrease BP: Reflex stimulate Sympathetic :
- Stimulate Heart : Tachycardia & Angina. (ADD beta-Blocker).
- Kidney: increase Renin & Edema. (ADD Diuretic).

b- Like Thiazide : Hyperglycemia (decrease Insulin release) & Hyperuricemia.

Uses

a-EMERGENCY Hypertension: Diazoxide is highly bound to plasma proteins so given by either:

Rapid IV injection of large dose.
Repeated IV injection of small doses till saturation of plasma proteins, then IV Infusion.

b-Orally in Hypoglycemia caused by Insulinoma

Sodium Nitroprusside

Very Powerful **MIXED (Balanced)** VD.

Mechanism of Action

Nitroprusside : RBCs & Endothelium : release NO : stimulate Guanylate Cyclase: ++ cGMP:

a-Mixed Balanced (Arteriolar = Venular) VD.

b- Inhibit Platelet aggregation.

A c t i o n s

a- Arterial VD: decrease TPR, decrease After-Load, decrease BP

b- Venous VD: decrease VR, decrease EDV, and decrease Pre-load, decrease BP

c- COP is maintained due to decrease of TPR. It may increase in patients with H.F.

TABLE 11-3 Mechanisms of action of vasodilators.

Mechanism	Examples
Release of nitric oxide from drug or endothelium	Nitroprusside, hydralazine, nitrates,[1] histamine, acetylcholine
Reduction of calcium influx	Verapamil, diltiazem, nifedipine
Hyperpolarization of smooth muscle membrane through opening of potassium channels	Minoxidil, diazoxide
Activation of dopamine receptors	Fenoldopam

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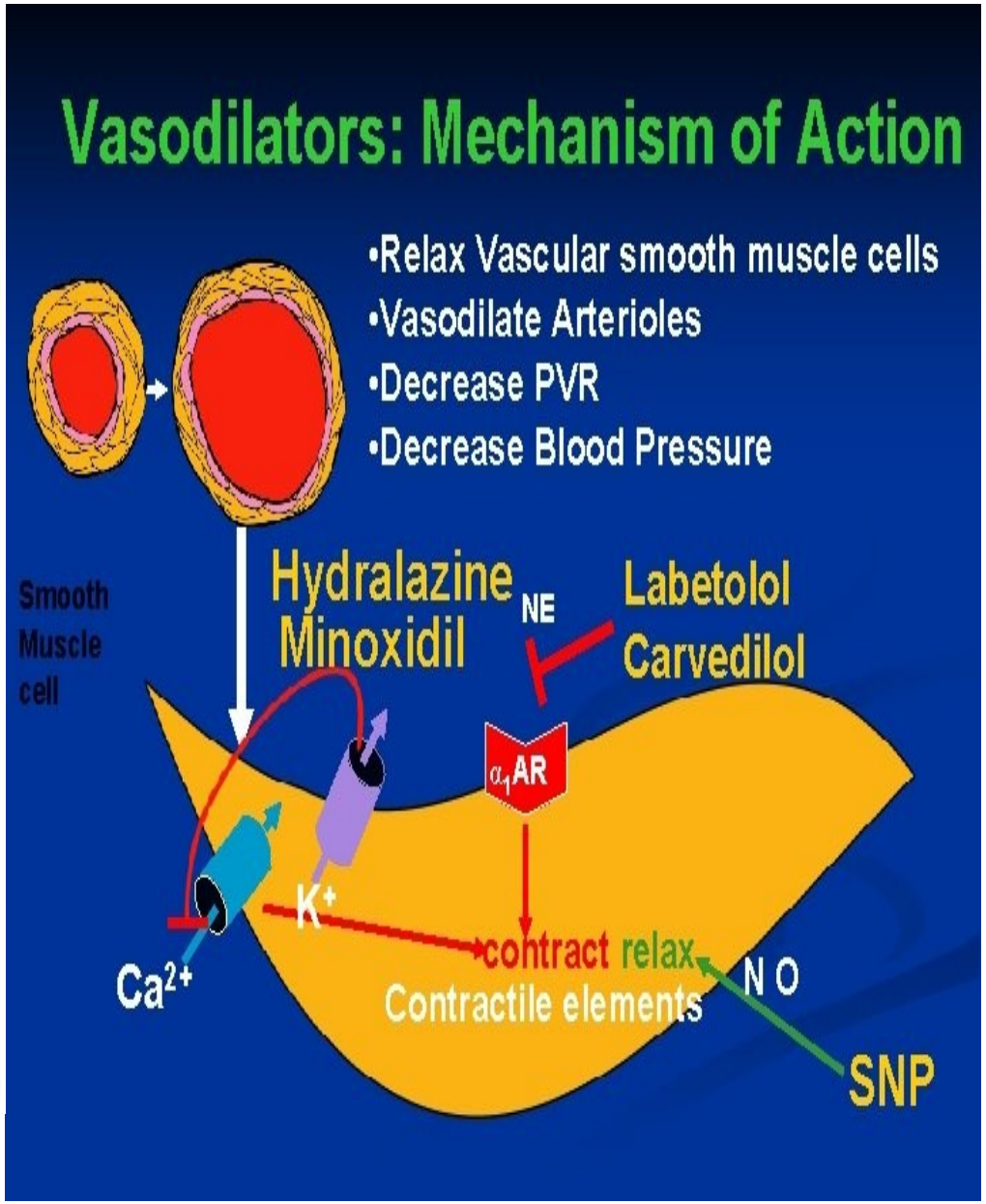

1. Identify the mechanism of action of alpha methyl dopa in the treatment of hypertension
2. List the uses and adverse effects of hyralazine

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.